## On the use of immunological Correlates for demonstration of protective efficacy of meningococcal conjugate vaccines.

VRBPAC - September 15, 1999

The purpose of the meeting is to discuss the ability to use immunologic correlates to demonstrate efficacy of meningococcal conjugate vaccines for the purpose of licensure. Additionally, our presentation is intended to alert the advisory committee that meningococcal conjugate vaccines are now in clinical studies. It is in the interests of the United States to be able to have such vaccines available in the US. But, as you know, a vaccine must be shown to be both safe and effective to be licensed. The latter element is the subject of the presentation before the VRBPAC.

The major question is can we use immunological correlates to demonstrate the effectiveness of meningococcal conjugate vaccines? While the question of immunological correlates apply to all meningococcal serogroups, the group C conjugate may be of greater interest, because at this time group C is the leading cause of meningococcal disease in the US and group C is the conjugate for which we have the largest amount of information.

The group C polysaccharide vaccine was first licensed in the US in 1976, combined with the meningococcal group A polysaccharide, then in 1981 with the A,Y, and W135 polysaccharides. Licensure was based upon randomized controlled efficacy trials in adults and children (see Chapter 28 in *Vaccines* 3rd edition, W.B. Saunders, 1999). The bivalent and quadravalent vaccines are recommended for use in people down to 2 years of age. However, vaccuine effectiveness is lower in children under 5 years of age. A meta analysis by Gonzalez et al (1997) of vaccine trials conducted with the group C polysaccharide gave an efficacy of 85% among adults and children over 5 years of age. Between 2 and 5 years of age the efficacy was 70% (95% CI 5-91%), and 55% among children 2-3 years of age.

Clinical studies are in progress to evaluate the safety and immunogenicity of group C meningococcal polysaccharide-protein conjugate vaccines. The incidence of meningococcal disease is usually quite low, about 1/100,000 total population, but this greatly increases during outbreaks. Since the occurrence of meningococcal outbreaks are unpredictable, and the normal incidence of the disease in the US is low, use of immune correlates must be considered. Data will therefore be presented on the association of bactericidal antibody with protection and on the use of bactericidal titers and ELISA antibody measurements as a indicator of protective immunity. It may be that the correlates of protection are good enough to substitute for clinical efficacy trials.

Immunity to meningococcal disease is mediated by *bactericidal antibodies*. The critical role of these antibodies has been demonstrated in a number of ways:

1. The highest incidence of meningococcal disease occurs in infants between 6 and 12 months of age. They have the lowest levels of bactericidal antibodies.

2. Studies by Goldschneider et al. (1969) in US Army recruits showed a direct correlation between susceptibility to meningococcal disease and absence of serum antibodies.

3. Individuals deficient in complement components C5, C6, C7 or C8 have markedly increases in susceptibility to systemic meningococcal disease.

In addition, as noted above the polysaccharide vaccine induces protective antibodies. Thus:

The capsular polysaccharide vaccine for meningococcus group C is approximately 80 to 90% effective in older children and adults.

These individuals are protected via induction of anti-capsular antibodies.

Immunization of adults with the group C polysaccharide induces bactericidal antibodies.

Therefore: The presumption is that induction of these bactericidal antibodies mediates the observed vaccine effectiveness.

Presentations by three vaccine manufactures will show that meningococcal conjugate vaccines are being manufactured and are being extensively clinically evaluated. A group C conjugate vaccine was the control vaccine for the recently reported Northern California Kaiser pneumococcal 7 valent conjugate efficacy studies, in which the vaccine was safely administered to about 18,000 infants. Meningococcal conjugate vaccines will soon be in general use in the United Kingdom. The following press release illustrates those manufactures most likely to be interested in marketing a conjugate vaccine:

"U.K. to Launch Meningitis C Vaccine in October"
Reuters (July 20, 1999)

"Britain's Health Minister Frank Dobson announced on July 20 that the National health Service would launch in October a campaign to provide the new conjugate vaccine against meningitis C infection. Initially, the vaccine will be supplied by Wyeth Laboratories, with Chiron Biocine and North American Vaccines also expected to join as suppliers at the beginning of next year. The program will target high-risk populations, which include babies and young people."

Another factor for consideration in the decision making process is a recently reported problem with the group C polysaccharide vaccine. This is the observed induction of a persistent hyporesponsiveness state following immunization of adults, toddlers and infants (see references below). The hyporesponsiveness was demonstrated by reimmunization of persons who had previously received the group C meningococcal polysaccharide vaccine with the polysaccharide again. Their responses were much lower than those of age matched controls receiving the polysaccharide for the first time. In a recent follow-up to their infant studies, MacDonald et al (presented at 1999 SPR and submitted to JAMA) reimmunized the children as toddlers. The infants had been given either two doses, two months apart, of a meningococcal group C conjugate vaccine or the plain polysaccharide. One year later these children were reimmunized with a group C conjugate to see if the conjugate vaccine would overcome the hyporesponsiveness seen in the polysaccharide immunized infants. Children who had received the conjugate vaccine were primed, and responded strongly. In contrast, the children who had previously received two doses of the polysaccharide vaccine had significantly lower ELISA and bactericidal responses than those who had received one dose of C polysaccharide, or the conjugate.

**Recent Meningococcal group C polysaccharide References**


1. Twumasi PA, Jr., Kumah S, Leach A, O'Dempsey TJD, Ceesay SJ, Todd J, Broome CV, Carlone GM, Pais LB, Holder PK, et al. A trial of a group A plus group C meningococcal polysaccharide- protein conjugate vaccine in African infants. J.Infect.Dis. 1995;171:632-8.

2. Leach A, Twumasi PA, Kumah S, Banya WS, Jaffar S, Forrest BD, Granoff DM, LiButti DE, Carlone GM, Pais LB, et al. Induction of immunologic memory in gambian children by vaccination in infancy with a group A plus group C meningococcal polysaccharide- protein conjugate vaccine. J.Infect.Dis. 1997;175:200-4.

3. Granoff DM, Gupta RK, Belshe RB, Anderson EL. Induction of immunologic refractoriness in adults by meningococcal C polysaccharide vaccination. J.Infect.Dis. 1998;178(3):870-4.

4. MacDonald NE, Halperin SA, Law BJ, Forrest B, Danzig LE, Granoff DM. Induction of immunologic memory by conjugated vs plain meningococcal C polysaccharide vaccine in toddlers - A randomized controlled trial. Journal of the American Medical Association 1998;280(19):1685-9.

5. Lepow ML, Perkins BA, Hughes PA, and Poolman JT. Meningococal vaccines. In: Plotkin SA and Orenstein WA (eds), Vaccines, 1999, SW. Saunders.

**Questions to be addressed by the advisory committee**

1. Can we use immunological correlates to demonstrate the effectiveness of meningococcal conjugate vaccines?
    a. Individuals for which the current polysaccharide vaccine is licensed.
    b. Infants below 12 months of age.

2. For both 1.a. and 1.b. can bactericidal antibodies be used as the measure of functional and therefore presumed protective activity?

3. Can total antibody quantitated by ELISA be used as a surrogate for functional bactericidal antibody, understanding that antibody levels associated with protection are not known.